REMARKS

Applicants have amended the specification on pages 13-14 and 22 as indicated hereinabove to indicate that murine hybridomas secreting monoclonal antibodies PA8, PA9, PA10, PA11, PA12 and PA14, respectively, rather that these antibodies *per se*, were deposited with the American Type Culture Collection (ATCC) under the indicated Accession Nos. Applicants note that these amendments are supported in the specification at, *inter alia*, page 26, lines 17-33, page 30, lines 12-29, and by the two ATCC deposit receipts, attached hereto as **Exhibit A**, confirming the December 2, 1998 deposit of these hybridomas. Thus, applicants maintain that these amendments to the specification do not raise any issue of new matter. Applicants therefore respectfully request that the Examiner enter these amendments into the application.

Claims 98-104 and 117-134 are pending in the subject application. By this Amendment, applicants have amended claims 98-102. Applicants note that claims 118 and 121-134 were newly presented in a Rule 312 Amendment filed December 22, 2003, but were not entered by the Examiner. Proposed amendments to claims 98 and 101 presented in the December 22, 2003 Amendment were also not entered.

The present amendments to claim 98 are supported in the specification at, *inter alia*, page 3, lines 24-25; page 4, lines 28-30; page 13, line 28 to page 14, line 8, as amended hereinabove; page 14, lines 26-30; page 17, lines 20-22 and 27-29; page 22, lines 5-11, as amended hereinabove; page 32, lines 18-20; page 33, lines 6-19, and page 38, lines 6-9. The amendments to claims 99 and 100 are supported in the

specification at, *inter alia*, page 13, line 28 to page 14, line 8, as amended hereinabove; page 22, lines 5-11, as amended hereinabove; page 26, lines 17-33 and page 30, lines 25-30. The amendments to claim 101 involve formatting changes which, *inter alia*, more precisely define the claimed monoclonal antibody or fragment thereof as "consisting of" rather than "comprising" CDRs derived from the PA14 hybridoma. The amendments to claim 102 merely involve minor formatting changes. Thus, applicants maintain that the above claim amendments do not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 98-104 and 117-134, as amended, will be pending and under examination.

Claim Objections

The Examiner stated that claim 99 is objected to because the claim recites "or fragment thereof" in line 7 of the claim and there is an internal lack of antecedent basis for this "fragment." The Examiner suggested that, to obviate this objection, this phrase should appear after "antibody" in line 2 of the claim. The Examiner stated that appropriate correction is required.

In response, applicants note that claim 99, as amended, is directed to a hybridoma cell line designated PA14 (ATCC Accession No. HB-12610) which produces a monoclonal antibody designated PA14, and does not recite the phrase "or fragment thereof." Accordingly, applicants respectfully submit that the above objection is moot.

Double Patenting

The Examiner provisionally rejected claims 98, 100-102 and 117 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 78 and 79 of copending Application No. 09/464,902.

The Examiner also provisionally rejected claims 98, 100-102, 117, 118 and 120 for obviousness-type double patenting as allegedly unpatentable over claims 1, 2 and 14 of copending Application No. 10/081,128.

The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because there is no patentable difference between an anti-CCR5 antibody designated PA14, or another antibody that binds to the same epitope as PA14, and the instant monoclonal antibody or fragment that binds to the same epitope as PA14. The Examiner also stated that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In response, and without conceding the correctness of the Examiner's position, applicants note that claims 78 and 79 in Application No. 09/464,902 were canceled in an Amendment filed October 4, 2004 (see reference 3 in the Supplemental Information Disclosure Statement included with the present Amendment). Applicants note also that U.S. Serial No. 10/081,128, filed February 22, 2002, has been abandoned pursuant to 37 C.F.R. 1.53(f) for nonpayment of the application fee and non-submission of a Declaration and Power of Attorney. Accordingly, applicants respectfully submit that

the provisional double patenting rejection is moot.

Rejections under 35 U.S.C. §102

The Examiner rejected claims 98-103, 117, 118, 123, 124, 129 and 130 under 35 U.S.C. §102(a) as allegedly anticipated by Wu et al. (WO 98/18826) ("Wu-1"). The Examiner stated that the claims are drawn to a monoclonal antibody or a fragment thereof comprising CDRs, where at least one CDR binds to an epitope of CCR5 in an N-terminal region and/or one of three extracellular loops of CCR5, wherein the antibody or the fragment binds to the same epitope as one of the antibodies, such as PA14, listed in instant claim 98. The Examiner further stated that the claims are also drawn to a hybridoma producing the instant antibody. The Examiner additionally stated that the claims also specify that the antibodies are humanized or chimeric, and comprise a framework of a human immunoglobulin molecule. The Examiner further noted that the claims also state that the antibody is a monovalent fragment.

In addition, the Examiner stated that Wu-1 teaches that monoclonal antibodies 5C7 and 3A9 are both specific for the N-terminus of the CCR5 receptor and that monoclonal antibody 2D7, which was generated from murine IgG1, has epitope specificity for the second extracellular loop of the CCR5 receptor (citing page 15, lines 18-21 and page 72, line 31, and claims 1-3, 27-29, 55, and 56). The Examiner also stated that the antibodies of Wu-1 comprise at least one CDR that binds to an epitope of CCR5 in an N-terminal region and/or one of three extracellular loops of CCR5, which would be the same epitopes recognized by at least one CDR in any of the instant antibodies claimed. The Examiner further stated that Wu-1 also teaches a bispecific

antibody that binds to the N-terminus and the second extracellular loop of CCR5 (citing page 15, line 27 to page 16, line 5), and humanized forms of the antibodies, where the framework and the consensus are derived from a human immunoglobulin or multiple immunoglobulin molecules, where the regions surrounding the CDR regions have been replaced by human immunoglobulin molecules (citing page 19, line 31 to page 21, line 32, and claims 1-7, 27-32, 47-50, 55 and 56).

In response, applicants respectfully traverse this rejection. Without conceding the correctness of the Examiner's position, applicants note that independent claims 98-101, as amended, are directed specifically to monoclonal antibody PA14 or a fragment thereof (claim 98), a hybridoma cell line which produces monoclonal antibody PA14 (claim 99), a monoclonal antibody or a fragment thereof which binds to the same epitope as monoclonal antibody PA14 (claim 100), and a monoclonal antibody or a fragment thereof consisting of CDRs derived from the PA14 hybridoma (claim 101). Applicants assert that monoclonal antibody PA14 is distinct from any of the monoclonal antibodies disclosed in Wu-1. This is evident, for example, from the fact that PA14 binds to an epitope of CCR5 which comprises a combination of amino acid residues in <u>both</u> the N-terminus (Nt) and the second extracellular loop (ECL2) of CCR5 (see the specification at, *inter alia*, page 33, lines 17-18), whereas the monoclonal antibodies taught by Wu-1 bind to epitopes comprising amino acid residues in the Nt (antibodies 5C7 and 3A9) <u>or</u> the ECL2 (antibody 2D7). Indeed, the subject specification discloses at page 33, lines 18-19 that monoclonal antibody 2D7 binds an epitope comprising Q170 and K171/E172 in the ECL2 region of CCR5, which is clearly a different epitope from that bound by PA14.

Applicants also emphasize that Wu-1's bispecific antibody recognizes two distinct epitopes, one in the Nt and one in the ECL2 region of CCR5, whereas applicants' PA14 antibody binds to a single epitope of CCR5 comprising a combination of amino acids in both the Nt and ECL2 region.

Applicants note that a finding of anticipation requires that a prior art reference teach each and every element of the rejected claims. Since Wu-1 does not teach an antibody which binds to a single CCR5 epitope comprising amino acids in both the Nt and ECL2 region as claimed in the present invention, applicants maintain that instant claims 98-101, as amended, are not anticipated by Wu-1.

Applicants note that rejected claims 102, 103, 117, 118, 123, 124, 129 and 130 which depend, directly or indirectly, from claims 98, 100 or 101, necessarily recite all the elements of claims 98, 100 or 101. Accordingly, applicants maintain that these dependent claims are also not anticipated by Wu-1.

The Examiner also rejected claims 98, 100, 101, 123 and 124 under 35 U.S.C. §102(b) as allegedly clearly anticipated by Wu et al. (J. Exp. Med. [1997] 186(8): 1373-1381) (Wu-2). The Examiner stated that the claims are drawn to a monoclonal antibody that binds to the N-terminus or one of the three extracellular loops of CCR5. The Examiner also stated that Wu-2 teaches a monoclonal antibody, murine IgG1 2D7, which binds to the second extracellular loop of CCR5 and another monoclonal antibody, 3A9, which binds to the N-terminal region of CCR5 (citing the second paragraph of the second column on page 1374 and the paragraph bridging the columns on page 1375).

In response, applicants respectfully traverse this rejection under 35 U.S.C. §102(b). As noted hereinabove in discussing the rejection under 35 U.S.C. §102(a), applicants reiterate that the instant claims, as amended, are directed specifically to monoclonal antibody PA14 or a fragment thereof (claim 98), a monoclonal antibody or a fragment thereof which binds to the same epitope as PA14 (claim 100), and a monoclonal antibody or a fragment thereof consisting of CDRs derived from the PA14 hybridoma (claim 101). For the reasons set forth above, applicants maintain that monoclonal antibody PA14 is distinct from monoclonal antibodies 2D7 and 3A9 disclosed in Wu-2. Thus, applicants also maintain that instant claims 98, 100 and 101, as amended, are not anticipated by Wu-2. In addition, claims 123 and 124 which depend from claims 100 and 101, respectively, necessarily recite all the elements of claims 100 and 101. Accordingly, applicants respectfully submit that claims 123 and 124 are also not anticipated by Wu-2.

For the above reasons, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 98-103, 117, 118, 123, 124, 129 and 130 under 35 U.S.C. §102(a) and (b).

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 104, 119-122, 125-128 and 131-134 under 35 U.S.C. §103(a) as allegedly obvious over Wu et al. (WO 98/18826) ("Wu-1"). The Examiner stated that the claims recite that the instant antibody comprises a human immunoglobulin molecule selected from IgG1, IgG2, IgG3, IgG4, IgA and IgM (citing the teachings of Wu-1 referred to above). The Examiner also stated that Wu-1 does not teach the

framework of the monoclonal antibodies to be IgG1, IgG2, IgG3, IgG4, IgA, or IgM. The Examiner stated that it would, however, have been obvious for one of ordinary skill in the art at the time the invention was made to obtain the antibody framework from any of the human immunoglobulins to maintain the conformation of the CDR region and to render the recombinant antibodies less immunogenic once administered. The Examiner also stated that, further, one of ordinary skill in the art would have been motivated to maintain the donor amino acid sequences immediately adjacent to the CDR domains to assure that when the framework portion of the antibody is added, the CDR domain remains intact. The Examiner additionally stated that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because humanizing antibodies using human IgG is a conventional technique for humanizing recombinant antibodies. The Examiner concluded that the invention as a whole would therefore have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

In response, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness of claims 104, 119-122, 125-128 and 131-134. Applicants note that in accordance with M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of obviousness, and to do so, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge of a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art

reference, or references when combined, must teach or suggest all the claim limitations.

Applicant maintains that the Examiner has failed to satisfy all three prongs of the requirements for establishing a *prima facie* case of obviousness. As noted above, the invention claimed in the instant independent claims, as amended, encompasses monoclonal antibody PA14 or a fragment thereof, a hybridoma cell line which produces monoclonal antibody PA14, a monoclonal antibody or a fragment thereof which binds to the same epitope as PA14, and a monoclonal antibody or a fragment thereof consisting of CDRs derived from the PA14 hybridoma. Monoclonal antibody PA14 is not a bispecific antibody and is clearly distinct from monoclonal antibodies 2D7 and 3A9 disclosed in Wu-1, which does not teach any of the PA 14-related elements of the claimed invention. Moreover, Wu-1, in combination with routine skill, does not provide any suggestion or motivation to make the claimed invention, nor does this reference provide any expectation of success in making it.

Applicants note that claims 104, 119-122, 125-128 and 131-134, which are rejected as allegedly obvious over Wu-1 all depend, directly or indirectly, from independent claims 98, 100 and 101. Since these dependent claims necessarily recite all the elements of claims 98, 100 and 101, applicants respectfully maintain that claims 104, 119-122, 125-128 and 131-134 are also not obvious over Wu-1.

Conclusion

In view of the remarks and explanations set presented hereinabove, applicants respectfully request that the Examiner

reconsider and withdraw the claim rejections and objections set forth in the August 25, 2004 Office Action, and earnestly solicit allowance of all claims pending in the subject application, namely, claims 98-104 and 117-134, as amended.

Information Disclosure Statement

The Examiner stated that some of the applications listed in the IDS submitted June 3, 2004 were not considered because the applications were previously abandoned and would have no bearing on the instant case. The Examiner also noted that applicants state in the June 3, 2004 submission that a copy of the claims from certain pending applications listed were provided in Exhibits. The Examiner further stated that it is, however, not clear what happened to these Exhibits applicant discusses since they are unavailable to the Examiner.

Applicants note that the Examiner also stated during a November 22, 2004 telephone conference with Ashton Delauney, Esq. of the undersigned's office that the references cited in the June 3, 2004 IDS which had not been considered, as indicated by strikethrough on the returned June 3, 2004 PTO-1449 form, were abandoned applications which had no relevance to the claims pending in the subject application. The Examiner further stated that none of these unconsidered references therefore needed to be resubmitted except for the listing of allowed claims in U.S. Serial No. 10/323,314 if this application has issued as a patent.

In response, applicants maintain that the copies of references identified as Exhibits 1-36 and submitted to the Patent Office in the June 3, 2004 IDS were received by the Office. In support, applicants attach hereto as **Exhibit B** a copy of the postcard which accompanied the June 3, 2004 IDS and which was returned to applicants' undersigned attorney by the Patent Office. The postcard confirms receipt of Exhibits 1-36 by the Patent Office on June 3, 2004, as evidenced by the Patent

Office's stamp bearing that date.

Applicants also respectfully disagree with the Examiner's statements implying that abandoned applications are necessarily irrelevant to the patentability of the instant claims. Applicants attach hereto as **Exhibit C** a copy of the June 3, 2004 PTO-1449 form returned by the Examiner and containing strikethroughs to indicate the abandoned references which she has not considered. Applicants note that copies of these references are being resubmitted in the Supplemental IDS contained herein, so that they can be considered by the Examiner.

Applicants also note that the listings of pending claims on the returned PTO-1449 form (**Exhibit C**) have been initialed by the Examiner as having been considered, notwithstanding the Examiner's statement in the August 25, 2004 Office Action that copies of these pending claims were unavailable to her. Applicants therefore assume that the Examiner was able to access these pending claims from within the Patent Office and has indeed considered them. If, however, these pending claims have not been considered, applicants respectfully request that the Examiner so inform them, and they will resubmit copies of the relevant pending claims for the Examiner's consideration.

This Supplemental Information Disclosure Statement is submitted under 37 C.F.R. §1.97(c)(2) to supplement the Information Disclosure Statements filed January 7, 2005, August 12, 2004, July 22, 2004, June 3, 2004, September 3, 2003, June 3, 2003, June 14, 2001, and September 6, 2000 in connection with the subject application.

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit D**), and certain of which are attached hereto as **Exhibits 1-11**:

1. U.S. Patent No. 6,261,763 B1, issued July 17, 2001 to G.P. Allaway et al.;

2. V.M. Litwin et al., U.S. Patent Application Publication No. 2001/0046512 A1, published November 29, 2001;

3. Pending claims in W.C. Olson and P.J. Maddon, U.S. Serial No. 09/464,902, filed December 16, 1999 (**Exhibit 1**);

4. Pending claims in W.C. Olson et al., U.S. Patent Application Publication No. 2003/0228306 A1, published December 11, 2003 (**Exhibit 2**);

5. Pending claims in W.C. Olson et al., U.S. Patent Application Publication No. 2004/0228869 A1, published November 18, 2004 (**Exhibit 3**);

6. Allowed claims in T. Dragic and W.C. Olson, U.S. Serial No. 10/323,314, filed December 19, 2002 (**Exhibit 4**);

7. G.P. Allaway et al., U.S. Serial No. 08/627,684, filed April 2, 1996 (now abandoned) (**Exhibit 5**);

8. G.P. Allaway et al., U.S. Provisional Application No. 60/014,532, filed April 2, 1996;

9. G.P. Allaway et al., U.S. Serial No. 08/663,616, filed June 14, 1996 (now abandoned) (**Exhibit 6**);

10. G.P. Allaway et al., U.S. Provisional Application No. 60/019,715, filed June 14, 1996;

11. G.P. Allaway et al., U.S. Serial No. 08/673,682, filed June 25, 1996 (now abandoned) (**Exhibit 7**);

12. G.P. Allaway et al., U.S. Serial No. 08/665,090, filed June 14, 1996 (now abandoned) (**Exhibit 8**);

13. G.P. Allaway et al., U.S. Provisional Application No. 60/019,941, filed June 14, 1996;

14. G.P. Allaway et al., U.S. Serial No. 08/874,570, filed June 13, 1997 (now abandoned) (**Exhibit 9**);

15. G.P. Allaway et al., U.S. Serial No. 08/874,618, filed June 13, 1997 (now abandoned) (**Exhibit 10**);

16. W.C. Olson and P.J. Maddon, U.S. Serial No. 09/212,793, filed December 16, 1998 (now abandoned);

17. W.C. Olson and P.J. Maddon, U.S. Provisional Application No. 60/112,532, filed December 16, 1998; and

18. W.C. Olson et al., U.S. Serial No. 09/663,219, filed September 15, 2000 (**Exhibit 11**).

The Examiner is respectfully requested to make these references of record in the present application by initialing

and returning a copy of the enclosed Form PTO-1449.

37 C.F.R. §1.98(a)(2)(ii), as amended in the September 21, 2004 Final Rule, states that copies of U.S. patents and published patent applications need not be submitted to the Patent Office in an Information Disclosure Statement unless required by the Office. Therefore, pursuant to 37 C.F.R. §1.98(a)(2)(ii), copies of the above-cited U.S. patent and patent application publication (references 1 and 2) are not attached hereto.

37 C.F.R. §1.98(a)(2)(iii) provides that an Information Disclosure Statement shall include, for each cited pending U.S. application, a legible copy of the application specification including the claims and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion. Under 37 C.F.R. §1.98(c), when the disclosures of two or more patents or publications listed in an Information Disclosure Statement are substantively cumulative, a copy of one of the patents or publications may be submitted without copies of the other patents or publications, provided it is stated that these other patents or publications are cumulative. In accordance with 37 C.F.R. §1.98(c), copies of certain of the references listed above are not being attached hereto as Exhibits as they are cumulative.

Specifically, references 7 and 8 are cumulative to each other since each contains an identical disclosure. Therefore, a copy of reference 7 is not attached hereto.

References 9 and 10 are cumulative to each other since each

contains an identical disclosure. Therefore, a copy of reference 10 is not attached hereto.

References 12 and 13 are cumulative to each other since each contains an identical disclosure. Therefore, a copy of reference 13 is not attached hereto.

References 16, 17 and U.S. Serial No. 09/464,902 are cumulative to each other since each contains an identical disclosure except that Serial No. 09/464,902 contains an additional paragraph at the beginning of the application claiming the benefit of an earlier application, U.S. Provisional Application No. 60/112,532 (reference 17), and also provides the ATCC Accession Number for the PA10 antibody, which Accession Number is not provided in references 16 and 17. A copy of U.S. Serial No. 09/464,902 was submitted to the Patent Office as Exhibit 14 in the June 3, 2004 Supplemental IDS, and was considered by the Examiner. Therefore, copies of references 16 and 17 are not attached hereto.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

Pursuant to 37 C.F.R. §1.97(c)(2) and 1.17(p), a fee of one hundred and eighty dollars ($180.00) is required for filing the Supplemental Information Disclosure Statement filed herewith. A fee of five hundred and ten dollars ($510.00) is also required for a three-month extension of time for responding to the August 25, 2004 Final Office Action. Accordingly, a check in the total amount of SIX HUNDRED AND

NINETY DOLLARS ($690.00) is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

2/24/05
John P. White Date
Reg. No. 28,678